

METRONIDAZOLE IN HUMAN INFECTIONS WITH SYPHILIS*

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Metronidazole ("Flagyl", May and Baker), which has been in wide use for the treatment of trichomonal vaginitis for 6 years has also been shown to be highly effective in the treatment of Vincent's gingivitis (Shinn, 1962; Davies, McFadzean, and Squires, 1964; Shinn, Squires, and McFadzean, 1965).

While it has not been possible to determine the minimum inhibitory concentration (MIC) of the compound against the spirochaetes thought to be involved in the aetiology of Vincent's disease, it has been shown to be active against the cultivable Reiter treponeme against which the MIC is 0.02 µg./ml. (Davies and others, 1964) compared to benzyl penicillin 0.005 µg./ml.

These observations suggested that it might be effective against *Treponema pallidum*, although Scott-Gray and Murrell (1961) found no effect in a patient with primary syphilis who was given the drug for 48 hours (9 tablets, 1.8 g.).

The present paper describes further observations made on patients with syphilis.

Methods

Six consecutive patients with secondary syphilitic lesions (condylomata lata) and positive serological tests for syphilis who presented themselves for treatment at the Jane Furse Memorial Hospital were given metronidazole in high dosage, and the influence of this drug on healing and the presence of *T. pallidum* was assessed.

The patients were of the Pedi tribe and living in Sekhukhuniland. Syphilis was endemic in this region in the pre-penicillin era but it is now well controlled, and the routine testing of ante-natal patients reveals less than 0.5 per cent. to be sero-positive.

Initially the patients were weighed, their lesions were photographed, and blood was taken for serological study. Scrapings were obtained from the lesions, and examined in coverslip preparations by the darkfield technique. Thereafter, scrapings were obtained twice daily whilst

the patients were receiving metronidazole, and finally at 24-hourly intervals when at least a further 2 weeks had elapsed since the conclusion of the course of metronidazole. When skin healing was established, material for darkfield preparations was obtained from serum and tissue fluid obtained by deep surgical scraping at the site of the healing or healed lesion.

Metronidazole was administered in tablet form as "Flagyl" at approximately 6-hourly intervals, and the fact that the tablets had been consumed was recorded by a senior nurse. Nausea, vomiting, rigor, or fever was likewise noted.

Further photographs were taken at various times.

One patient had a second specimen of blood examined serologically one month after completing the course of metronidazole. Whilst patients were receiving metronidazole, daily total white cell and differential counts were done, and the film was examined for platelet content and red cell changes.

Dosage

The dosage of metronidazole posed a problem, since initial observations had shown 2 g. daily in divided doses to be inadequate, and at the time the individual blood level or cerebrospinal fluid (CSF) content were unknown. The rather arbitrary dosages shown in Table I were administered.

TABLE I
DOSAGE OF METRONIDAZOLE

Day	Daily Dose (g.)					
	Patient No.					
	1	2	3	4	5	6
1	2	2	2	3	2	2
2	2	4	4	4	4	4
3	4	4	4	4	4	4
4	3	4	4	4	4	4
5	2.5	4	4	4	3	4
6		4	4	4	4	4
7			4	4	4	4
8			4	4	4	4
9			4			
Total	13.5	22.0	34.0	27.0	29.0	30.0

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Before departing for their homes in distant places all patients received a full course of PAM (penicillin aluminium monostearate).

In order to get fuller information on the blood levels of metronidazole, three patients with trichomonal vaginitis were given the drug in high dosages and their blood was sampled at various intervals and assayed polarographically for metronidazole. The CSF content of metronidazole was estimated in one patient from the syphilitic group and also in one of the second group with trichomonal vaginitis.

Results

In all the syphilitic patients, healing was evident between the 4th and 7th day, and the lesions were dry and progressing towards complete epithelialization after from 7 to 9 days. After a further 2 weeks healing was complete, and in those in whom longer periods of observation were possible skin pigmentation was restored (Figs 1 and 2).

All showed very transient and isolated clinical features such as fever, nausea, vomiting, and rigor, resembling a modified Jarisch-Herxheimer reaction.

A slight transient relative lymphocytosis was constantly observed to develop in the syphilitic patients while they were receiving metronidazole, but no changes in red cells or platelets were detected.

Spirochaetes morphologically characteristic of *T. pallidum* and also displaying the customary motility of this micro-organism were initially present in the material from all patients. The presence of a variety of other organisms was also marked at the beginning of the experiment. The persistence of *T. pallidum* varied in individual patients (Table II, opposite). Two of the female patients were darkfield-negative by Day 3, two were negative by Day 4, and one became negative on Day 6. The one male patient did not become negative until Day 8.

In the three patients who were given 1 g. metronidazole four times daily for 24 hours, the serum and CSF samples showed high concentrations of the drug (Table III, opposite). The serum concentrations varied from 15 to 72 $\mu\text{g./ml.}$, and one CSF sample contained 80 $\mu\text{g./ml.}$ A second sample of CSF, taken from a patient with condylomata, had a concentration of 58 $\mu\text{g./ml.}$ after 7 days treatment with 1 g. four times daily.

All patients gave strong serological reactions for syphilis and in the quantitative Kolmer test this reached 160 units. The level had not fallen in the one patient (Case 3) in whom the test was repeated after an interval of one month.



FIG. 1.—Case 4 before treatment.



FIG. 2.—Case 4 one month after treatment, showing disappearance of lesions and repigmentation.

TABLE II
RESULTS OF DARKFIELD EXAMINATION FOR *T. PALLIDUM*

Day	Hour	Patient No.					
		1	2	3	4	5	6
1	09.00	—	—	—	+ ⁰	—	+ ²
	18.00	+ ³	+ ²	+ ⁰	+ ¹	+ ¹	+ ¹
2	09.00	+ ²	+ ⁰ F	+ ⁰	+ ¹ N	+ ¹ N	+ ²
	18.00	+ ⁰	+ ⁰ F	+ ⁰	+ ¹ NVF	+ ²	+ ⁰
3	09.00	+ ⁰ NVR	+ ⁰	+ ⁰	—ve	+ ¹ NV	+ ⁰
	18.00	+ ⁰	+ ¹	+ ²	—ve	+ ¹ NF	—ve
4	09.00	—ve	—ve	+ ³	—ve	+ ⁰	—veF
	18.00	—ve	—ve	+ ²	—ve	—ve	—ve
5	09.00	—ve	—ve	+ ¹ F	—ve	—ve	—veF
	18.00	—ve	—veH	+ ⁰	—veH	+ ⁰	—ve
6	09.00	—veF	—ve	—ve	—ve	—ve	—ve
	18.00	—ve	—ve	+ ⁰ F	—ve	—veH	—ve
7	09.00	—ve	—ve	+ ⁰ H	—ve	—ve	—veF
	18.00	—ve	—ve	+ ⁰	—ve	—ve	—ve
8	09.00	—ve	—ve	+ ⁰	—ve	—ve	—ve
	18.00	—ve	—ve	—ve	—ve	—ve	(CSF sample)
9	09.00	—ve	—ve	—ve	—ve	—ve	—ve
	18.00	—ve	—ve	—ve	—ve	—ve	—ve

Final observations at least 14 days after the last dose of metronidazole and at 24 hr intervals.

1st Specimen	09.00	—ve	—ve	—ve	—ve	—ve	—ve
2nd Specimen	09.00	—ve	—ve	—ve	—ve	—ve	—ve

CLASSIFICATION	H	Healing.	+ ⁴	Masses.
	F	Febrile.	+ ³	A large number.
	N	Nausea.	+ ²	A fair number.
	V	Vomiting.	+ ¹	A few.
	R	Rigor.	+ ⁰	Scanty.

TABLE III

LEVELS OF METRONIDAZOLE IN THE SERUM AND CSF IN THREE PATIENTS GIVEN 1 g. FOUR TIMES A DAY

Time of Dosage	Patient No.								
	3566			3631			3612		
	Dose (g.)	Time of Serum Sample	Concentration (μg./ml.)	Dose (g.)	Time of Serum Sample	Concentration (μg./ml.)	Dose (g.)	Time of Serum Sample	Concentration (μg./ml.)
		11.08	0.0					11.00	0.0
12.00	1.0			Nil	12.10	0.0	1.0		
18.00	1.0	18.05	15.7	1.0	19.0	0.0	1.0	18.00	15.7
24.00	1.0	00.45	61.5	1.0	01.05	44.1	1.0	01.00	34.2
06.00	1.0	06.00	45.7	Nil	07.00	26.7	1.0	06.05	72.5
12.00	1.0	12.00	52.8	1.0	13.00	32.1	1.0	13.03	46.8
					17.00	28.1			
								[CSF 14.30	80.4]

Discussion

Local signs of healing and the elimination of *T. pallidum* followed the pattern of similar lesions treated with penicillin but was much slower.

The side-effects were mild, transient, and hap-hazard and more in the nature of a modified Jarisch-Herxheimer reaction than of drug side-effects. A further factor supporting such a conclusion was the subsequent good tolerance of continued administration of metronidazole.

In patients given 200 mg. three times daily for 7 days for the treatment of trichomonal vaginitis, and in whom treatment was successful, serum concentrations of the drug varied from 3.6 to 9.8 μg./ml.

(Kane, McFadzean, Squires, King, and Nicol, 1961). This dosage schedule had no effect on the lesions of secondary syphilis.

In vitro the cultivable Reiter's strain of *T. pallidum* is inhibited by 0.02 μg./ml. metronidazole, but concentrations of 5.2 μg./ml. are required to cause 50 per cent. immobilization of the Nichols strain (Wilkinson, 1965). However, it would appear that much higher serum concentrations of the drug are required to produce significant effects on clinical syphilis.

The influence of metronidazole in the serum on the *Treponema pallidum* immobilization (TPI) test is being investigated at present (Wilkinson, 1966).

With the highly effective and long-established treatment of syphilis with penicillin, metronidazole is unlikely to make any real contribution to therapy in this disease.

The Pedi are extremely co-operative as patients and a similar tolerance to this drug should not be too readily assumed in more sophisticated people.

Summary

Metronidazole in high dosage has been shown to bring about local healing and disappearance of the treponemes in secondary syphilitic lesions.

The interference of sera containing metronidazole with the performance of TPI tests is postulated.

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REFERENCES

- Davies, A. H., McFadzean, J. A., and Squires, A. (1964). *Brit. med. J.*, **1**, 1149.
 Kane, P. O., McFadzean, J. A., Squires, S., King, A. J., and Nicol, C. S. (1961). *Brit. J. vener. Dis.*, **37**, 273.
 Scott-Gray, M., and Murrell, M. (1961). *Practitioner*, **186**, 218.
 Shinn, D. L. S. (1962). *Lancet*, **1**, 1191.
 —, Squires, S., and McFadzean, J. A. (1965). *Dent Practit.*, **15**, 275.
 Wilkinson, A. E. (1965). Personal communication.
 — (1966). Personal communication.

La métronidazole dans les infections syphilitiques chez l'homme

RÉSUMÉ

Il a été démontré que la métronidazole à fortes doses guérit les lésions syphilitiques secondaires et fait disparaître les tréponèmes de ces lésions.

L'interférence du sérum contenant de la métronidazole et les résultats des tests de l'immobilisation du tréponème sont considérés.